PATENT SPECIFICATION

NO DRAWINGS

1,058,384

1,058,384

Date of Application and filing Complete Specification: June 11, 1964.
No. 7518/66.
Application made in United States of America (No. 287783) on June 14, 1963.
(Divided out of No. 1058383)
Complete Specification Published: Feb. 8, 1967.

Index at acceptance:—C2 C(1E7C1, 1E7E1, 1E7H2, 1E7N3, 1F4B, 1F4C2, 1F4C3, 1F4C4, 1F4D2, 1F4D3, 1F4F2, 1F4F4, 1F4F5, 2B2A2, 2B2A3, 2B2F, 2B2G3, 2B2G9, 2B6A2, 2B6B, 2B6G4, 2B6J, 2B29, 2B36, 2B38)

Int. Cl.:—C 07 c 129/12, C 07 d 85/22

COMPLETE SPECIFICATION

Guanidinoarylcarboxylic Acids and their Halides

We, MERCK & Co. INC., a body corporate duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with certain novel guanidino-substituted organic acids and their halides. These compounds are useful as acylating agents in the preparation of novel acylated penicillin compounds which are claimed in the specification of our copending application No. 24287/64 Serial No. 1058383.

The compounds provided by this invention have the general formula R.CO.X, where X is a halogen atom or a hydroxy radical and R is a guanidinoaryl, guanidinomethylaryl, guanidinoaralkyl, guanidinoaryloxyalkyl, guanidinomethylaralkyl, guanidinomethylaryloxyalkyl, guanidinoarylisoxazolyl or guanidinomethylarylisoxazolyl radical.

In accordance with the present invention, these compounds are prepared by a method as set forth below from the appropriate amino acid by replacing the amino group with a guanidino substituent, and recovering the resulting guanidino-substituted carboxylic acid from the reaction mixture. The acid will in general be recovered initially in the form of an acid-addition salt, but this can be converted to the free guanidino acid by suitable adjustment of the pH. The corresponding acid halide is prepared by reaction of the thus-obtained guanidinocarboxylic acid with a halogenating agent of a type known to be capable of converting a carboxylic acid to an acid halide i.e. a halogenating agent which is in use or whose use is described in the literature for that purpose. Thionyl chloride in the presence of a teritary amine is a suitable halogenating agent.

In accordance with the invention, the guanidino-substituted carboxylic acid may be prepared from the corresponding amino-substituted carboxylic acid by contacting the selected amino acid with *S*-methylisothionitrourea to yield as an intermediate product the corresponding nitroguanidinocarboxylic acid, which is then converted by catalytic hydrogenation to the desired guanidino-substituted carboxylic acid. The guanidino-substituted carboxylic acid prepared in this manner may be converted to the corresponding acid chloride, e.g., by reaction with thionyl chloride.

In accordance with a preferred method of preparing guanidinoarylcarboxylic acids, guanidinoaralkylcarboxylic acids, and guanidinoisoxazolyl carboxylic acids, the selected amino carboxylic acid is intimately contacted with benzoyl cyanamide and the resulting product hydrolysed to the desired guanidinoaryl, guanidinoaralkyl, or guanidinoisoxazolyl carboxylic acid. Thus, for example, *p*-guanidinobenzoic acid is prepared by intimately contacting *p*-aminobenzoic acid and benzoyl cyanamide followed by hydrolysis of the reaction product, 5-methyl-3-(*p*-guanidinophenyl)-4-isoxazolyl carboxylic acid is prepared by the reaction of 5-methyl-3-(*p*-aminophenyl)-4-isoxazolyl-carboxylic acid and benzoyl cyanamide followed by hydroylsis of the reaction product to yield the desired guanidino-substituted acid, and *p*-guanidinophenylacetic acid is prepared by contact-

[*Price* 4*s.* 6*d.*]

ing *p*-aminophenylacetic acid with benzoyl cyanamide followed by hydrolysis of the resulting reaction product to the desired guanidino acid.

In a preferred method of preparing the guanidinomethylarylcarboxylic acids and the guanidinomethylaralkylcarboxylic acids, the selected aminoethylarylcarboxylic acid or the aminomethylaralkylcarboxylic acid is reacted with *O*-methylisourea in alkaline solution to produce the corresponding guanidinomethylarylcarboxylic acid or guanidinomethylaralkylcarboxylic acid. Thus, for example, *p*-guanidinomethyl-benzoic acid is prepared by reaction of *p*-aminomethylbenzoic acid and *O* methylisourea in alkaline solution, and *p*-guanidinomethylphenylacetic acid is similarly obtained from *p*-aminomethylphenylacetic acid.

In accordance with the above procedures, the following novel guanidino-substituted carboxylic acids, the corresponding acid halides, and their salts, are readily prepared from the corresponding amino acids 2-phenyl-4-guanidinobenzoic acid; 4-guanidino-2-ethoxy-1-naphthoic acid; 2,6-dimethoxy-4-guanidinobenzoic acid; 2-phenyl-4-guanidinomethylbenzoic acid; 4-guanidinomethyl-2-ethoxy-1-naphthoic acid; 2,6-dimethoxy-4-guanidinomethylbenzoic acid; 4-guanidinophenylacetic acid; 4-guanidinophenoxyacetic acid; 2-(4-guanidinophenoxy)-propionic acid; 5-methyl-3-(4-guanidinophenyl)-4-isoxazolylcarboxylic acid; *p*-guanidinophenyl-α-aminoacetic acid; 2-(4-guanidinophenoxy)-butyric acid; 5-methyl-3-(2-chloro-4-guanidinophenyl) -4- isoxazolylcarboxylic acid; 4-guanidinomethylphenylacetic acid; 4-guanidinomethylphenoxyacetic acid; 2-(4-guanidinomethylphenoxy)-propionic acid; 5-methyl-3-(4-guanidinomethylphenyl) -4- isoxazolylcarboxylic acid; *p*-guanidinomethylphenyl -α- aminoacetic acid 2-(4-guanidinomethylphenoxy)-butyric acid; 5-methyl -3-(2-chloro -4- guanidinomethylphenyl)-4-isoxazolylcarboxylic acid. By reaction of an acid from the foregoing list with a halogenating agent, e.g., thionyl chloride, there is formed the corresponding acid halide or its salt, e.g, 2-phenyl-4-guanidinobenzoyl chloride hydrochloride.

The invention is illustrated by the following Examples, in which all percentages are by weight.

Example 1

p-Guanidinobenzoyl chloride hydrochloride

A solution of 1.5 g. of *p*-aminobenzoic acid and 1.62 g. of benzoyl cyanamide in 5 ml. of ethanol is evaporated to dryness at steam bath temperature. An additional 5 ml. of ethanol is added and the evaporation repeated in a similar manner. The residue is stirred for one hour in 5% aqueous sodium bicarbonate solution, and filtered, To the filtrate is added 4 equivalents of sodium hydroxide, and the resulting solution maintained at reflux temperature for approximately 20 minutes. The solution is then decolorized with activated charcoal and to the decolorized filtrate is added an additional 6 equivalents of sodium hydroxide, and maintained at room temperature for approximately 30 minutes. Acidification of the solution with glacial acetic acid effects crystallization of *p*-guanidinobenzoic acid, which is recovered by filtration and dried.

A mixture is prepared containing 5 cc. of thionyl chloride, 3 drops of pyridine, and 537 mg. *p*-guanidinobenzoic acid. The mixture is heated and stirred for approximately 1 hour and benzene is added to precipitate the formed *p*-guanidinobenzoyl chloride hydrochloride. The precipitate is recovered by centrifugation and dried under vacuum.

Example 2

5-Methyl -3- (*p*-guanidinophenyl) -4- isoxazolyl carboxylic acid

To a stirred solution of 50 g. *p*-nitrobenzaldehyde in 500 ml. pyridine is added 25.3 g. hydroxylamine hydrochloride. The solution which forms is heated for approximately 1 hour at steam bath temperature. To the solution is added 3 volumes of water and the solution cooled until the product, *p*-nitrobenzaldoxime, crystallizes from solution. The crystalline product is recovered by filtration and recrystallized from an ethanol-water mixture.

52 g. *p*-nitrobenzaldoxime is suspended in 202 ml. of 8.3N aqueous hydrochloric acid and the resulting mixture cooled to 0°C. Chlorine gas is bubbled through the solution for approximately 1 hour, whereupon crystalline *p*-nitrobenzaldoxime chloride crystallizes from solution and is recovered by filtration.

To a solution of 18.2 g. sodium methoxide in 113 ml. of methanol is added rapidly 44 g. ethyl acetoacetate. After stirring the solution for approximately 10 minutes, it is cooled to −25°C.

A solution of 51 g. *p*-nitrobenzaldoxime chloride in 113 ml. methanol is cooled to approximately 10°C. and added to the previously-prepared solution of ethyl acetoacetate at a rate such that the temperature of the reaction mixture is held below 0°C. with cooling. The resulting mixture is stirred for approximately 18 hours at 25°C, whereupon an orange precipitate of ethyl [5-methyl -3- (*p*-nitrophenyl) -4- isoxazolyl] carboxylate precipitates and is recovered by filtration. The recovered product is washed with methanol and water and purified by recrystallization from a methanol-ether mixture.

A solution of 43 g. of ethyl [5-methyl-3-(*p*-nitrophenyl)-4-isoxazolyl] carboxylate in

755 ml. of methanol is heated to reflux temperature under an atmosphere of nitrogen, and to it is added a solution of 167 ml., 1N aqueous sodium hydroxide, and the temperature maintained at reflux for approximately 1½ hours. The solution is then cooled to 25°C, 20 ml. of concentrated glacial acetic acid is added, and the solution is concentrated *in vacuo* until the product precipitates. Water is added to the reaction mixture to complete precipitation of the product which is recovered from solution by filtration, washed and dried. Recrystallization from ethanol gives substantially pure 5-methyl -3- (*p*-nitrophenyl(-4-isoxazolyl carboxylic acid.

To 1 g. of 5% rhodium-on-carbon catalyst, which is pre-reduced with hydrogen, is added a solution of 2.4 g. 5-methyl-3-(*p*-nitrophenyl)-4-isoxazolyl carboxylic acid in 250 ml. methanol. The resulting mixture is agitated continuously and hydrogenated under 40 pounds hydrogen pressure until hydrogenation appears to be substantially complete. The catalyst is removed from the solution by filtration and the solvent removed by concentration *in vacuo*, leaving the product as a residue. The residue is dissolved in ether and triturated with methanol. Further purification by extraction with ethyl acetate and removal of the solvent yields substantially pure 5-methyl(*p*-aminophenyl)-4-isoxazolylcarboxylic acid.

973 mg. of 5-methyl-3-(*p*-aminophenyl)-4-isoxazolylcarboxylic acid and 362 mg. of benzoyl cyanamide are mixed in 5 ml. of ethanol and the solution evaporated to dryness at steam bath temperature. Addition of 5 ml. of ethanol to the residue and evaporation to dryness are repeated twice. The residue from the reaction mixture is suspended in 5% aqueous sodium bicarbonate solution, stirred for approximately 1 hour and filtered to remove unreacted starting material. To the filtrate is added approximately 250 mg. of sodium hydroxide and the resulting solution heated at reflux temperature in an atmosphere of nitrogen for approximately 15 minutes. The resulting solution is decolorized with activated charcoal and subsequently treated with approximately 750 mg. of sodium hydroxide and stirred at 25°C for approximately 30 minutes. The product, 5-methyl-3-(*p*- guanidinophenyl) -4- isoxazolylcarboxylic acid is precipitated by neutralization of the alkaline solution with glacial acetic acid. The precipitated product is recovered by filtration and recrystallized from hot water.

EXAMPLE 3

p-Guanidinophenoxyacetic acid hydrochloride

A mixture of 1.4 g. of *p*-aminophenoxyacetic acid and an aqueous solution of sodium hydroxide containing approximately 10 milliequivalents of sodium hydroxide, 2 ml. dimethyl formamide and 1.4 g. of *S*-methylisothionitrourea are stirred at 60°C for 1.5 hours. The resulting solution is cooled and 10 milliequivalents of dilute hydrochloric acid is added to precipitate the formed *p*-nitroguanidinophenoxyacetic acid. The product is recovered by filtration, air dried and dissolved in aqueous sodium hydroxide. The sodium hydroxide solution is filtered to remove extraneous material and washed with ethyl acetate. Substantially pure *p*-nitroguanidinophenoxyacetic acid is crystallized from the aqueous solution by acidification and cooling. The crystalline material is recovered by filtration and dried. m.p. 239°C. (d).

7.3 g. of *p*-nitroguanidinophenoxyacetic acid is dissolved in 450 ml. of 90% aqueous methanol and reduced with hydrogen at 40 pounds per square inch hydrogen pressure in the presence of 4.5 g. of 10% palladium-on-carbon catalyst until approximately 4 moles of hydrogen are taken up. The catalyst is removed from the reaction mixture by filtration and washed with methanol. The solid catalyst mixture is extracted with boiling water to dissolve the reduced product and filtered. The filtrate containing the product is concentrated to a small volume and treated with dilute hydrochloric acid to produce *p*-guanidinophenoxyacetic acid hydrochloride, which is recovered by evaporating the aqueous solution to dryness *in vacuo* m.p. 170°C. It can be converted to the acid itself by procedures analogous to those described in Example 2.

EXAMPLE 4

p-Guanidinomethylbenzoic acid hydrochloride

A solution of 2 g. of *p*-cyanobenzoic acid in 40 ml. of ethanol saturated with ammonia, and 2 g. Raney nickel catalyst are hydrogenated at 85°C under 1500 pounds per square inch of hydrogen pressure. The hydrogenation reaction mixture is filtered to remove the catalyst and the product recovered from the filtrate by acidification with 2.5N HCl, whereupon crystalline *p*-aminomethylbenzoic acid precipitates from solution and is recovered by filtration.

A solution of 1.2 g. of *p*-aminomethylbenzoic acid in 16 ml. of water containing 3.76 ml. of concentrated ammonium hydroxide is prepared and mixed with 2.26 g. of *O*-methylisourea hydrochloride. The resulting reaction mixture is stirred for about 18 hours and filtered to remove the precipitated product. The product is dissolved in hot aqueous ethanol and reprecipitated by acidification of the solution to pH 2. The resulting product, substantially pure *p*-guanidinomethylbenzoic acid hydrochloride, is recovered by filtration and dried. It can be converted

to the acid itself by procedures analogous to those described in Example 2.

Following the procedures described in Example 4, *p*-cyanophenylacetic acid is converted by catalytic hydrogenation to *p*-aminomethylphenylacetic acid which is, in turn, reacted with *O*-methylisourea hydrochloride in concentrated ammonium hydroxide to produce *p*-guanidinomethylphenylacetic acid which is isolated as the hydrochloride, which can then, if desired, be converted to the acid itself.

EXAMPLE 5

p-Guanidinophenylacetic acid

To a solution of 6.04 g. of *p*-aminophenylacetic acid in 50 ml. of water and 15 ml. of 2.7N sodium hydroxide is added 5.4 g. of finely-ground 1-nitro-2-methylisourea. The mixture is stirred at room temperature for 16 hours, filtered, and then carefully acidified with cooling. The product which crystallizes out is recrystallized from water, giving 4.4 g. of *p*-nitroguanidinophenylacetic acid m.p. 188—190°C.

1 g. of Raney nickel is added to a hot solution of 2.0 g. of *p*-nitroguanidinophenylacetic acid in 75 ml. of methanol and the mixture is refluxed for 15 minutes. The combined filtered solution and washings (79 ml.) is mixed with 1 g. Raney nickel and hydrogenated at approximately 40 pounds per square inch pressure at 25°C. Hydrogen absorption is complete after three hours. The hydrogenation reaction mixture is filtered to remove the catalyst. The filtrate, containing *p*-guanidinophenylacetic acid, is evaporated to dryness *in vacuo*, and the residue crystallized from water. The first crop weighs 550 mg., gives a positive Sakaguchi test, and melts with decomposition at 320—2°C.

EXAMPLE 6

2,6-Dimethoxy-4-guanidinobenzoic acid hydrochloride

A mixture of 11 g of 4-bromo-2,6-dimethoxy-benzoic acid and 3.7 g. of potassium carbonate and 6 ml. of benzyl bromide in 100 ml. of acetone is heated at the reflux temperature of the mixture for approximately 20 hours. The reaction mixture is filtered and the filtrate containing the product benzyl-4-bromo-2,6-dimethoxybenzoate evaporated to remove the acetone solvent, leaving the product as an oily residue. The product is purified by dissolving in 100 ml. ether, washing with aqueous sodium bicarbonate, and removal of the ether and unreacted benzyl bromide by concentration under reduced pressure (100°C at 0.1 mm.) for approximately one hour to obtain the product as a residue.

To a solution of sodium amide prepared by the reaction of 1.2 g. sodium and 200 ml. liquid ammonia is added, with stirring 11 g. of benzyl-4-bromo-2,6-dimethoxybenzoate, and stirring is continued for approximately 3½ hours. To the reaction mixture is added 3.5 g. of ammonium chloride, and the ammonia removed by evaporation. The residue containing the product benzyl-4-amino-2,6-dimethoxybenzoate is extracted with a mixture of 150 ml. ether and 150 ml. water, and the undissolved product recovered by filtration. Additional product is obtained from the ether extract by back extraction with aqueous dilute sulphuric acid. The aqueous acid extract is then neutralized to precipitate additional product. The combined product is then recrystallized from methanol. m.p. 115—116°C. The N.M.R. spectrum confirms that the thus-obtained product is benzyl 4-amino-2,6-dimethoxybenzoate.

A mixture of 574 mg. of benzyl 4-amino-2,6-dimethoxybenzoate and 324 mg. of benzoyl cyanamide in 5 ml. of ethanol is heated at steam bath temperature for 30 minutes, during which time the ethanol evaporates. The residue is diluted with an additional 5 ml. of ethanol and evaporation and heating are continued for an additional 1½ hours. The residual material is then contacted with 5 ml. ethanol and 0.5 ml. of 11.7N sodium hydroxide solution and the resulting mixture heated for approximately 45 minutes and then allowed to stand at 25°C. for approximately 18 hours. The residue thus obtained is dissolved in 20 ml. water and the water solution of the product washed with 20 ml. of ether. The aqueous solution of the product is acidified to about pH 2 and washed with ether to remove benzoic acid. The aqueous solution is then concentrated to 10 ml. and neutralized with aqueous sodium bicarbonate to precipitate 2,6-dimethoxy-4-guanidinobenzoic acid which is recovered by filtration and washed with water. The product thus obtained melts with decomposition at about 220°C.

The product thus obtained is dissolved in 1 ml. of aqueous hydrochloric acid and the solution evaporated to dryness to obtain as a residue 2,6-dimethoxy-4-guanidinobenzoic acid hydrochloride which is crystallized by stirring with acetone and recovered by filtration and washed with ether. m.p. dec. 220°C

WHAT WE CLAIM IS:—

1. A compound having the general formula R. CO.X where X is a halogen atom or a hydroxy radical and R is a guanidinoaryl, guanidinomethylaryl, guanidinoaralkyl, guanidinoaryloxyalkyl, guanidinomethylaralkyl, guanidinomethylaryloxyalkyl, guanidinoarylisoxazolyl or guanidinomethylarylisoxazolyl radical.

2. 5-Methyl-3-(*p*-guanidinophenyl)-4-isoxazolylcarboxylic acid.

3. *p*-Guanidinophenoxyacetic acid.
4. *p*-Guanidinomethylbenzoic acid.
5. *p*-Guanidinomethylphenylacetic acid.
6. *p*-Guanidinophenylacetic acid.
7. 2,6-Dimethoxy-4-guanidinobenzoic acid.
8. Salts of the compounds claimed in claims 1—7.
9. A process for preparing a compound of formula R—COOH, where R is as defined in claim 1, that comprises contacting the corresponding aminoaryl, aminomethylaryl, aminoaralkyl, aminoaryloxyalkyl, aminoethylaralkyl, aminomethylaryloxyalkyl, aminoarylisoxazolyl or aminomethylarylisoxazolyl carboxylic acid with *S*-methylisothionitrourea to yield as an intermediate product the corresponding nitroguanidinocarboxylic acid, and catalytically hydrogenating the latter.
10. A process for preparing a compound of formula R—COOH, where R is a guanidinoaryl, guanidinoaralkyl or guanidinoarylisoxazolyl or guanidinomethylarylisoxazolyl radical that comprises intimately contacting the corresponding aminoaryl, aminoaralkyl, aminoarylisoxazolyl or aminomethylarylisoxazolyl carboxylic acid with benzoyl cyanamide and hydrolysing the resulting product.
11. A process for preparing a compound of formula R—COOH, where R is a guanidinomethylaryl or guanidinomethylaralkyl radical, that comprises reacting the corresponding aminomethylaryl or aminomethylaralkyl carboxylic acid with *O*-methylisourea in alkaline solution.
12. A process as claimed in any one of claims 9—11, including the further step of reacting the resulting acid with a halogenating agent (as hereinbefore defined) of a type known to be capable of converting carboxylic acids to their halides, to produce a compound of formula R—CO(halogen), where R is as defined in claim 1.
13. A process for preparing a compound as claimed in claim 1, substantially as hereinbefore described with reference to any one of the foregoing examples.
14. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 9—13 or by an obvious chemical equivalent of such a process.

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Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1967.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.